AMENDED SPECIFICATION

Reprinted as amended in accordance with the Decision of the Superintending Examiner acting for the Comptroller-General dated the twenty-sixth day of April, 1961, under Section 29, of the Patents Act, 1949. Reference has also been directed in pursuance of Sections 8 and 9 of the Act.

PATENT SPECIFICATION

NO DRAWINGS

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International Classification:—C07d.

COMPLETE SPECIFICATION

Improvements in or relating to New Perfluoroalkylphenothiazine Derivatives

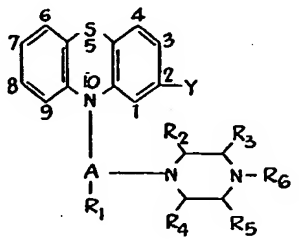
We, SMITH KLINE & FRENCH LABORATORIES, a corporation organized under the laws of the Commonwealth of Pennsylvania, one of the United States of America, of 1530 Spring Garden Street, City of Philadelphia, Commonwealth of Pennsylvania, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is performed, to be particularly described in and by the following statement:—

This invention relates to new 10-(piperazinylalkyl) - perfluoroalkylphenothiazine derivatives. The novel compounds of this invention are of value as therapeutic agents.

More specifically, the compounds of this invention have utility as antiemetics, tranquilizers, antihistaminics, spasmolytics, antishock agents and potentiators of various drugs such as analgetics and anesthetics. When used as tranquilizers, these compounds have the ability to abate mental disturbances such as anxiety, confusion or excitation without physical incapacitation. In addition, these compounds have chemotherapeutic or antimicrobial activity, such as antibacterial and fungicidal activity. Further, the novel compounds of this invention have a surprisingly low degree of toxicity.

The compounds of this invention are 10-(piperazinylalkyl) - perfluoroalkylphenothiazine derivatives represented by the general formula:

FORMULA I.



wherein:

Y represents perfluoroalkyl of 1 to 3 carbon atoms, preferably —CF_3,

A represents a straight or branched alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms,

R_1 is H,

R_2, R_3, R_4 and R_5 each represent methyl, ethyl or hydrogen,

R_6 represents the following:

cycloalkyl of 5 or 6 carbon atoms, for example, cyclopentyl and cyclohexyl;

cycloalkylalkyl of from 6 to 10 carbon atoms, such as β-cyclohexylethyl and β-cyclopentylmethyl;

alkenyl of from 2 to 6 carbon atoms such as allyl and isocrotonyl;

dialkylamino - lower - alkyl having one to six carbon atoms in each of the alkyl por-

tions and 2 to 6 carbon atoms in the lower alkyl portion, preferably dimethyl or diethylamino-lower-alkyl, for example dimethylaminobutyl and diethylaminoethyl;

hydroxy - lower - alkyl of from 2 to 6 carbon atoms, for example, hydroxyethyl and hydroxybutyl;

hydroxy - lower - alkyl - oxy - lower - alkyl, the lower alkyl portions having 2 to 6 carbon atoms, for example, ω-hydroxyethoxyethyl and ω-hydroxypropoxypropyl;

phenyl; cinnamyl; furoyloxybutyl; furoyl; thenyl;

monocyclic aralkyl having 2 to 6 carbon atoms in the alkyl portion, for example, *phenyl-lower*-alkyl, such as benzyl, phenethyl and ω-phenylbutyl;

aliphatic acyl of from 1 to 6, preferably 1 to 4 carbon atoms, for example, formyl, acetyl, butyryl, propionyl, caproyl, isocaproyl, or crotonyl or halogenated derivatives of said aliphatic acyls such as chloroacetyl, trifluoroacetyl, heptafluorobutyryl and dichloroacetyl; *alicyclic aliphatic acyl of from 7 to 10 carbon atoms*, such as cyclopentylpropionyl, hexahydrobenzoyl and cyclohexylbutyryl; *monocyclic aryl-aliphatic acyl of from 6 to10 carbons*, such as cinnamoyl, phenylacetyl, phenylpropionyl or benzoyl; *carbomethoxy; carbethoxy; carbobenzoxy; carbamyl;*

dialkyl carbamyl having 1 to 6 carbon atoms in the alkyl portions such as diethylcarbamyl or dimethylcarbamyl; *N-phenyl carbamyl;*

aliphatic - acyloxy - lower - alkyl having from 1 to 6, preferably from 2 to 4 carbon atoms in the acyloxy portion and 2 to 6 carbon atoms in the lower alkyl portion, such as acetoxyethyl, crotonoyloxyethyl, butyryloxybutyl or isocaproyloxyethyl and *monocyclic aroyloxy - lower - alkyl* having 2 to 6 carbon atoms in the lower alkyl portion such as benzoyloxy-lower-alkyl. Any of the acyl moieties defined above under "acyl" can be used as substituents on the oxygen atom of the hydroxy-lower-alkyl moieties.

The values of Y, A, R_1, R_2, R_3, R_4, R_5 and R_6 in Formula I should be chosen so that in any one compound, when Y is CF_3, A is propylene and R_1, R_2, R_3, R_4 and R_5 are each hydrogen, R_6 is not hydroxy-lower-alkyl having 2 or 3 carbon atoms in the alkyl portion, nor aliphatic acyloxy-lower-alkyl having 1 to 6 carbon atoms in the acyloxy portion and 2 or 3 carbon atoms in the lower alkyl portion.

Advantageous compounds of this invention are represented by the above structural formula when:

Y repreesnts trifluoromethyl,

A represents ethylene, propylene or 2-methyl-propylene,

R_2, R_3, R_4 and R_5 represent hydrogen, and

R_6 represents hydroxy - lower - alkyl, aliphatic acyloxy - lower - alkyl or hydroxy-lower - alkyl - oxy - lower alkyl. When A represents ethylene or 2-methylpropylene, and hydroxyl - lower - alkyl having 4 to 6 carbon atoms in the alkyl portion, aliphatic acyloxy-lower-alkyl having 1 to 6 carbon atoms in the acyloxy portion and 4 to 6 carbon atoms in the lower alkyl portion, or hydroxy-lower-alkyl-oxy-lower-alkyl, when A represents propylene.

By the term "alkyl" where used herein, aliphatic groups having not more than 6 carbon atoms and, preferably not more than 4 carbon atoms, is intended except where otherwise specifically indicated.

The term "lower alkyl" is used in connection with alkylene residues and as thus used represents aliphatic groups of from 2 to 6 carbon atoms, preferably 2 to 4 carbon atoms except where otherwise specifically indicated.

This invention also includes salts of the above defined bases formed with non-toxic organic and inorganic acids. Such salts are easily prepared by methods known to the art. The base is reacted with either the calculated amount of organic or inorganic acid in water-miscible solvent, such as acetone or ethanol, with isolation of the salt by concentration and cooling, or an excess of the acid in water-immiscible solvent, such as ethyl ether or chloroform, with the desired salt separating directly. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, pamoic, succinic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, *p*-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids as well as with the 8-halotheophyllines, for example, 8-chlorotheophylline and 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids. Of course, these salts may also be prepared by the classical method of double decomposition of appropriate salts which is well known to the art.

The compounds of this invention are prepared using 2 - perfluoroalkylphenothiazine starting materials which are prepared by methods well-known to the art and most readily by classical methods of phenothiazine formation, such as thionation of properly substituted 2-perfluoroalkyldiphenyl amines, namely, the Bernthsen reaction. Reference may be had to "S. P. Massie, Chemical Reviews, 54; 794 (1954)".

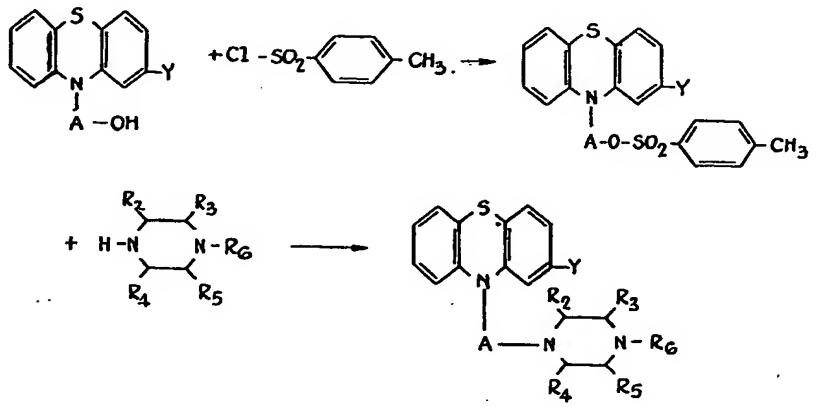
The 2 - perfluoroalkylphenothiazine nucleus is condensed with a reactive piperazinylalkyl ester having the desired piperazinylalkyl group. The condensation is carried out by refluxing the reactants in an inert aromatic solvent, such as benzene, xylene or toluene, in which at least

one of the reactants must be soluble. A suitable acid-binding agent may be included, such as an alkali metal amide, preferably sodium amide or potassium amide; an alkali metal hydroxide, preferably potassium hydroxide; an alkali metal hydride, preferably sodium hydride; or alkali metal aryl or alkyl compounds, preferably phenyl sodium.

The piperazinylalkyl ester is preferably used as the free base although the acid addition salts may be used with a corresponding increase in the amount of inorganic base as defined above. Any reactive piperazinylalkyl ester containing the desired substituted piperazinylalkyl group may be used, such as the halides, preferably bromide or chloride, or the sulfonic or sulfuric esters, preferably the *p*-toluene sulfonate.

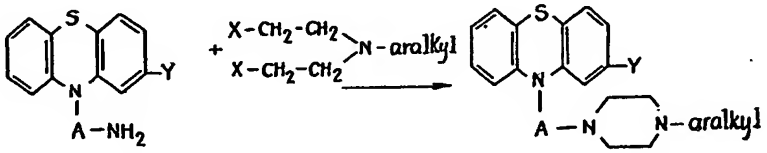
The 10 - (piperazinylalkyl) - perfluoroalkylphenothiazines are alternatively prepared by methods which involve chemical modifications of an alkyl chain which has a reactive, terminal group such as a halogen, a carboxy, tosylate, aldehydo or cyano group and which is attached to the 10-position of the parent 2-perfluoroalkylphenothiazine. Such methods are conveniently used to prepare 10 - (N - substituted-piperazinylalkyl) - 2 - perfluoroalkylphenothiazines and are particularly valuable for the preparation of the piperazines unsubstituted at the terminal N position which are useful intermediates for the preparation of the compounds of this invention. These synthetic procedures will be more evident from the following description.

For example, the 2 - perfluoroalkylphenothiazines substituted in the 10-position with an alkyl chain containing a terminal reactive ester group, such as tosylate, are prepared as in the following procedure. A 2-tetrahydropyranyl ether of a haloalkanol is condensed in an inert solvent, such as xylene, with a 2-perfluoroalkylphenothiazine in the presence of an acid binder, such as sodamide, to give a 10-(ω - tetrahydropyranyloxy - alkyl) - 2 - perfluoroalkylphenothiazine. The protective pyranyl group is removed with acid, for example, hydrochloric acid. The resulting 10-(ω - hydroxyalkyl) - 2 - perfluoroalkylphenothiazine derivatives is then esterified with an appropriate acyl halide, such as tosyl (*p*-toluene sulfonyl) chloride to give the desired reactive ester, in this case the tosylate. The resulting ester is reacted with a piperazine, preferably at reflux in alcohol with a mild alkali. This procedure is illustrated in the following scheme:



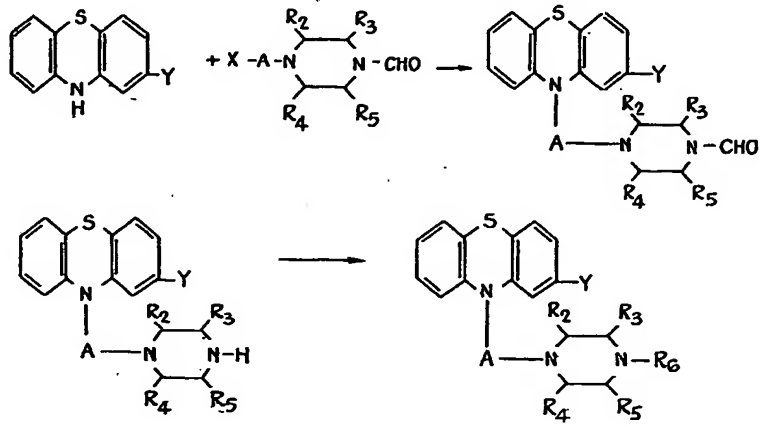
It is, at times, convenient to react the 10-(ω - hydroxyalkyl) - perfluoroalkylphenothiazine derivative obtained as hereafter described with a reactive inorganic halide, such as thionyl chloride, thionyl bromide or phosphorus pentachloride, in a non-ionic solvent, such as benzene or xylene, to give a 10 - (ω - haloalkyl) - perfluoroalkylphenothiazine which is then reacted with a piperizine preferably in excess or in the presence of an acid binder, such as sodium carbonate in an aqueous alcohol medium.

As a further example of the preparation of these compounds, certain 10 - (ω - piperazinylalkyl) - 2 - perfluoroalkylphenothiazine derivatives are prepared from the terminal primary amine derivatives by condensing a 10-(ω-aminoalkyl) - 2 - perfluoroalkylphenothiazine (made readily by reduction of the ω-cyanoalkyl analogue) with a substituted bis - (β-haloalkyl) - amine, such as an aralkylbis - (β-haloalkyl) - amine, to give a 10 - [ω - (N-substituted - piperazinyl) - alkyl] - perfluoroalkylphenothiazine such as a 10 - [ω - (N-aralkylpiperazinyl) - alkyl] - perfluoroalkylphenothiazine as specifically illustrated in the following scheme showing the formation of the N-aralkylpiperazinyl derivatives.



X as used in the above and following scheme equals halogen.

The compounds of Formula I where R_6 is an easily removed group such as an acyl group are useful intermediates for preparing other N-substituted compounds of this invention by hydrolysis followed by reaction with reactive esters such as bromides, iodide or chlorides or with ethylene oxide. This route of synthesis conveniently gives compounds of this invention in good yield and purity which would be obtained otherwise with more difficulty. For example, the production of 10 - (N - substituted - piperazinylalkyl) - 2 - perfluoroalkylphenothiazines may be accomplished by protecting the nitrogen of the piperazinylalkyl ester with a formyl group by the following procedure:



The monosubstituted piperazine is heated at reflux with an excess of a formic acid ester, such as methyl or ethyl formate. The volatiles are removed *in vacuo* and the desired N-formylpiperazinylalkyl ester isolated by distillation or fractional crystallization. Optionally, the N-formylpiperazinylalkyl ester may be formed by reversing the order of reaction, for instance by N - formulating ω - hydroxy-lower - alkylpiperazine and then reacting with thionyl chloride to form N - (ω - chloro-lower - alkyl) - N - formylpiperazine. This N-formyl ester is reacted with 2 - perfluoroalkylphenothiazine to give 10-[ω-(N-formylpiperazinyl) - alkyl] - 2 - perfluoroalkylphenothiazine. The protective formyl group is removed by mild hydrolysis conditions, such as with dilute sodium hydroxide solution, to give the desired 10 - (ω - piperazinylalkyl) - 2-perfluoroalkylphenothiazine. Alternatively, the protecting group may be a benzyl group which cannot be removed by hydrolysis but will be removed by catalytic hydrogenation.

This compound is further N-substituted by alkylation methods, such as with a reactive ester as discussed above in the presence of base, for instance with a substituted alkyl halide with potassium carbonate. Alternatively, hydroxy alkylation can be accomplished by reaction with an alkylene oxide such as ethylene oxide, or alklation by N-acylation followed by reduction of the resulting amide, for instance by reduction with lithium aluminum hydride in tetrahydrofuran.

The foregoing is a general description of the main synthetic routes in the preparation of 10 - (ω - piperazinylalkyl) - 2 - perfluoroalkylpheothiazine derivatives. It will be readily apparent to one skilled in the art that variations of these procedures are possible. Of particular advantage as preparative procedures are the first two methods discussed, namely, substitution of 2 - perfluoroalkylphenothiazine in the 10-position of the nucleus by reaction with a reactive piperazinylalkyl ester, and utilization of 2 - perfluoroalkylphenothiazine derivatives substituted in the 10-position with aliphatic chains containing a reactive terminal group.

It will be readily apparent to one skilled in the art that certain of the compounds of this invention, notably those in A is represented by an aliphatic carbon chain branched so that an asymmetric carbon atom is formed or where the ω-piperazinyl moiety is C-substituted, may be present as optical or cis-trans isomers. The

connotation of the general formulae presented herein is to include the separated *d* or *l* optical isomers as well as the *dl* mixture of these isomers. If desired, the isomers may be separated for individual use by separation methods known to the art, such as fractional crystallization of the *d*-tartrate salts of the perfluoroalkylphenothiazine derivatives. Alternatively, a synthesis starting with an optically active side chain may yield the desired optical isomer.

The following examples will be illustrative of compounds of this invention and the procedures for their preparation and will serve to make fully apparent all of the compounds embraced by the general formula given above and the preparation thereof respectively.

EXAMPLE 1.

A suspension of 69.0 g. of 2 - trifluoromethylphenothiazine in 1 l. of toluene with 10.0 g. of sodium amide is heated at reflux with high speed stirring for 15 minutes. A solution of 54.1 g. of 1 - formyl - 4 - (3^1 - chloropropyl) - piperazine, [prepared by formylating 1 - (3^1 - hydroxypropyl) - piperazine by refluxing in an excess of methyl formate, purifying the 1 - formyl - 4 - (3^1 - hydroxypropyl) - piperazine by vacuum distillation, reacting this compound with an excess of thionyl chloride at reflux and isolating the desired 1 - formyl - 4 - (3^1 - chloropropyl)-piperazine by neutralization with sodium carbonate solution followed by distillation] in 200 ml. of toluene is added. The reflux period is continued for four hours. The cooled reaction mixture is treated with 200 ml. of water. The organic layer is extracted twice with dilute hydrochloric acid. The acid extracts are made basic with ammonia and extracted with benzene. The volatiles are taken off *in vacuo* at the steam bath to leave a dark brown oil which is 10-[3^1-N-formylpiperazinyl)-propyl]-2-trifluoromethylphenothiazine. It can be distilled at 260° C. at 10 microns, or used directly without distillation if desired.

EXAMPLE 2.

A solution of 33 g. of 10 - (2^1 - chloroethyl)-2 - trifluoromethylphenothiazine (prepared by the reaction of ethylene oxide with 2-trifluoromethylphenothiazine followed by subsequent treatment of the β - hydroxyethyl compound with thionyl chloride) and 25 g. of anhydrous piperazine in 200 ml. of isoamyl alcohol is heated at reflux for twelve hours. The reaction mixture is then washed well with water. The organic layer is extracted with dilute hydrochloric acid. After neutralizing with ammonia and extracting with ethyl acetate, drying and evaporating the acetate extracts gives 5 g. of the crude base, 10 - (2^1 - piperazinylethyl) - 2 - trifluoromethylphenothiazine.

A suspension of 3.9 g. of 10 - (2^1 - piperazinylethyl) - 2 - trifluoromethylphenothiazine, 2.0 g. of 2 - bromo - 1 - diethylaminoethane and 0.5 g. of sodium amide in 50 ml. of benzene is heated at reflux with stirring for six hours. The reaction mixture is isolated by the procedure of Example 1. The crude syrup, 10 - [2^1 - (β - N - diethylaminoethylpiperazinyl) - ethyl] - 2 - trifluoromethylphenothiazine, is purified by molecular distillation, at 195° C. at 1 micron.

EXAMPLE 3.

A solution of 24.0 g. of 10 - (3^1 - hydroxypropyl) - 2 - trifluoromethylphenothiazine *p*-toluene sulfonate, (prepared by reacting 2 - trifluoromethylphenothiazine with γ - bromopropyltetrahydropyranyl ether, removing the protective group with mineral acid and acylatin with tosyl chloride in pyridine), 20.0 g. of N-hydroxyethoxyethylpiperazine in 300 ml. of ethanol with 10.0 g. of potassium carbonate is heated for six hours with stirring. The solution is diluted with water, evaporated *in vacuo* and extracted with ethyl acetate. The dried oragnic extract is evaporated to leave a crude syrup of 10 - [3^1 - N - hydroxyethoxyethylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine.

EXAMPLE 4.

Heptafluoropropylbenzene (180 g.) is slowly added to a mixture of nitric acid (d. 1.5) and concentrated sulfuric acid while maintaining the temperature at 20—30° C. The reaction mixture is quenched in an ice slurry, taken up in benzene and dried. Distillation at 100° C. at 10 mm. gives 1 - heptafluoropropyl - 3 -nitrobenzene. A mixture of 125 g. of this compound in 300 ml. of purified dioxane is reduced with hydrogen at 2,000 p.s.i. in the presence of 15 g. of Raney nickel catalyst. Dilution with benzene, filtering the catalyst and evaporation gives a residue 3-heptafluoropropylaniline, b.p. 95 to 96° C., at 12 mm.

Equivalent amounts of potassium carbonate, 2-chlorobenzoic acid and the anile with 5.0 g. of copper powder in 500 ml. of amyl alcohol are heated at reflux with stirring for 24 hours. The basic reaction mixture is subjected to steam distillation. The residue is an aqueous slurry of the desired product as the sodium salt, 2-(3^1 - heptafluoropropylphenylamino) - benzoic acid. The free acid is obtained by trituration with excess dilute hydrochloric acid.

The water-washed aminobenzoic acid (225 g.) is decarboxylated by heating at 200° C. until the evolution of carbon dioxide ceases. A mixture of 33.5 g. of the resulting crude solid, 3 - heptafluoropropyldiphenylamine, and 17.4 g. of sulfur and 0.3 g. of iodine is heated at 160—180° C. until the evolution of hydrogen sulfide ceases. The reaction mass is then extracted with hot benzene. Concentration and cooling separates greenish yellow platelets of 2 - heptafluoropropylphenothiazine.

A suspension of 20.0 g. of 2-heptafluoropropylphenothiazine, 12.0 g. of 3-chloro-1-(N - hydroxyethylpiperazinyl) - propane and 3 g. of potassium carbonate in 300 ml. of toluene is heated at reflux for four hours. After

working up the mixture as in Example 1, a viscous syrup, 2 - heptafluoropropyl - 10 - [3¹-(N - hydroxyethylpiperazinyl) - propyl]-phenothiazine, is obtained by molecular distillation.

A solution of 2.0 g. of this base in 25 ml. of ethyl acetate is reacted with a slight excess of maleic acid in ethyl acetate. Concentration and cooling gives the dimaleate salt.

EXAMPLE 5.

A solution of 103.5 g. of 10-[3¹-(N-formylpiperazinyl - propyl] - 2 - trifluoromethylphenothiazine (made as in Example 1) in 400 ml. of ethanol and 218 ml. of water containing 26 ml. of 40% sodium hydroxide solution is heated at reflux for two hours. The alcohol is taken off *in vacuo* on the steam bath. The residue is swirled with benzene and water. The dried benzene layer is evaporated *in vacuo*. The residue is vacuum distilled to give a viscous, yellow oil, 10-(3¹-piperazinyl - propyl) - 2 - trifluoromethylphenothiazine, distilling at 210—235° C. at 0.5 to 0.6 mm. A suspension of 7.8 g. of 10-(3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine (made in the above manner), 3.4 g. of ω-bromobutanol and 8.0 g. of potassium carbonate in 150 ml. of xylene is heated at reflux with stirring for five hours. After working up the reaction mixture as in Example 4, and distilling the crude basic residue, a viscous syrup is obtained, 10 - [3¹ - (N - ω-hydroxybutylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine.

A solution of 1.1 g. of the base is dissolved in 25 ml. of pyridine and 0.5 ml. of butyryl chloride is added. After standing at room temperature for 12 hours, the reaction mixture is quenched. The separated product is washed well with water, dried *in vacuo* and taken up in ethyl acetate ether. Dry hydrogen chloride gas is passed through the solution to separate crystals of 10 - [3¹ - (N - ω - butyryloxybutylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine dihydrochloride.

EXAMPLE 6.

A solution of 3.9 g. of 10 - (3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine (made as in Example 5), in 150 g. of benzene is swirled while 1.8 g. of phenylacetyl chloride is added dropwise. After standing overnight, the separated crystals of 10 - [3¹ - (N - phenylacetylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine hydrochloride are removed by filtration and washed with ether.

EXAMPLE 7.

A solution of 3.8 g. of 10 - (2¹ - piperazinylethyl) - 2 - trifluoromethylphenothiazine (made as in Example 2) in 150 g. of benzene with 4 ml. of pyridine is swirled while 3 ml. of acetic anhydride are added. The reaction mixture is allowed to stand overnight and evaporated to dryness. The residue after the usual acid extraction and neutralization, is taken up in ethyl acetate and reacted with one equivalent of maleic acid to give 10 - [2¹ - (N-acetylpiperazinyl) - ethyl] - 2 - trifluoromethylphenothiazine maleate.

EXAMPLE 8.

A solution of 8.6 g. of 10-[3¹-(N-hydroxyethylpiperazinyl)propyl] - 2 - trifluoromethylphenothiazine in 50 g. of pyridine is swirled as 3.0 g. of benzoyl chloride is added. The reaction mixture, after standing for eight hours, is poured into a large volume of water. The material which separates is washed well with water, taken up in ether, and treated with ethereal hydrogen chloride to give crystals of 10 - [3¹ - (N - benzoyloxyethylpiperazinyl)-propyl] - 2 - trifluoromethylphenothiazine dihydrochloride; melting point 226—228° C.

EXAMPLE 9.

A suspension of 26.7 g. of 2 - trifluoromethylphenothiazine, 25.0 g. of N-carbethoxy-N¹ - (γ - chloro - β - methylpropyl) - piperazine, prepared by condensing N - carbethoxypiperazine with 3 - bromo - 2 - methylpropylchloride, and 4.5 g. of sodium amide in 500 ml. of toluene is reacted and worked up following the procedure of Example 1 to leave a dark oil, 10 - [3¹ - (N - carbethoxypiperazinyl)-2¹ - methylpropyl] - 2 - trifluoromethylphenothiazine.

EXAMPLE 10.

A solution of 28.4 g. of 10 - [3¹ - (N-carbethoxypiperazinyl) - 2¹ - methylpropyl]-2 - trifluoromethylphenothiazine (made as in Example 9) in 300 ml. of aqueous ethanol and 15 ml. of 40% sodium hydroxide solution is heated at reflux for four hours. The alcohol is removed *in vacuo* and the residue is swirled with benezene and water. The dried benzene layer is evaporated. The thick residue is distilled to give a viscous, yellow, oil, 10-(2¹-methyl - 3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine, b.p. 210—215° C. at 0.1 mm. which solidifies upon standing.

A portion of this base, 2.9 g., is dissolved in 75 ml. of ethyl acetate and reacted with 3g. of mandelic acid in 50 ml. of ethanol. The mixture is allowed to evaporate on the steam bath until the salt begins to separate. Cooling yields 10 - (2¹ - methyl - 3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine dimandelate.

A second portion of the base, 2.9 g., is dissolved in 75 ml. of ethyl acetate and mixed with 5 ml. of alcoholic hydrogen bromide. Cooling gives the dihydrobromide salt of the base.

A solution of 5.7 g. of 10 - (2¹ - methyl-3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine, in 150 ml. of ethanol is warmed with 1.7 g. of ethylene oxide to 50° C. for one hour. The volatiles are removed *in vacuo* to leave 10 - [3¹ - (N - hydroxyethylpiperazinyl) - 2¹ - methylpropyl] - 2 - trifluoromethylphenothiazine.

A solution of 1.6 g. of the hydroxyethyl base in 50 ml. of ether-benzene is heated at

reflux with 1 ml. of acetyl chloride. The separated monohydrochloride of 10 - [3¹ - (N-acetoxyethylpiperazinyl) - 2¹ - methylpropyl]-2 - trifluoromethylphenothiazine is optionally isolated as such or shaken in an ethyl acetate-sodium carbonate solution mixture and converted to the dimaleate salt with an excess of maleic acid.

A solution of 1.6 g. of the hydroxyethyl base in 50 ml. of ether-benzene is heated at reflux with 0.8 g. of benzoyl chloride. The hydrochloride of 10 - [3¹ - (N - benzoyloxyethylpiperazinyl) - 2¹ - methylpropyl] - 2 - trifluoromethylphenothiazine is isolated as described above.

EXAMPLE 11.

A solution of 2.7 g. of 10 - (3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine (made as in Example 5) and 1.5 g. of benzoyl chloride in 125 ml. of benzene is heated at reflux for several hours. Concentration and standing yields crystals of the hydrochloride of 10 - [3¹ - (N - benzoylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine.

Another aliquot containing 2.7 g. of the base and 1.2 g. of 2-furoyl chloride is reacted and worked up as above to yield 10 - [3¹ - (N-furoylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine hydrochloride.

EXAMPLE 12.

A suspension of 36.7 g. of 2-heptafluoropropylphenothiazine (made as in Example 4), 4.0 g. of sodium amide and 27.5 g. of N-diethylcarbamyl - N¹ - (γ - chloropropyl)-piperazine (prepared by reacting N - diethylcarbamylpiperazine with γ - chloropropyl bromide in xylene with sodium amide in 300 ml. of toluene is heated at reflux for six hour. The reaction mixture is worked up following the procedure of Example I, but the hydrochloride salt is recovered and purified by crystallization to give 10 - [3¹ - (N - diethylcarbamylpiperazinyl) - propyl] - 2 - heptafluoropropylphenothiazine hydrochloride.

EXAMPLE 13.

A solution of 53.0 g. of crude 10 - [3¹ - (N-diethylcarbamylpiperazinyl) - propyl] - 2-heptafluoropropylphenothiazine hydrochloride (made as in Example 12) in 200 ml. of concentrated hydrochloric acid is heated at reflux for 10 hours. The solution is diluted with water and filtered. The filtrate is neutralized with 40% sodium hydroxide solution. The separated product is taken up in chloroform, dried and treated with hydrogen chloride gas to separate 2 - heptafluoropropyl - 10 - (3¹ piperazinylpropyl) - phenothiazine dihydrochloride.

A suspension of 5.8 g. of this salt in 50 ml. of toluene with 1.8 g. of β-bromoethyl acetate and 2.0 g. of potassium carbonate is heated at reflux, with stirring, for 12 hours. Water is added to the cooled mixture. The resulting organic layer is extracted into dilute hydrochloric acid. After neutralizing the extracts and taking the separated base up in benzene, a residue is obtained by evaporating the organic solvent *in vacuo*. This residue is chromatographed on alumina. The purified fraction of 10 - [3¹ - (N - acetoxyethylpiperazinyl)-propyl] - 2 - heptafluoropropylphenothiazine dihydrochloride is taken up in ethyl acetate and mixed with alcoholic hydrogen chloride. Concentration *in vacuo* enables crystals of the dihydrochloride salt to be recovered.

EXAMPLE 14.

A suspension of 2.6 g. of 10 - (3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine (made as in Example 5), 0. 5 g. of sodium amide and 1.4 g. of 4 - chloro - 1 - dimethylaminobutane in 50 ml. of toluene is heated at reflux for 24 hours. After working up as in Example I, the viscous base, 10 - [3¹ - (N-dimethylaminobutylpiperazinyl) - propyl] - 2-trifluoromethylphenothiazine is recovered.

A solution of 1.0 g. of this base in 50 ml. of ethanol is treated with 0.6 g. of methanesulfonic acid. Trituration with ether and cooling gives the trimethanesulphonate salt.

EXAMPLE 15.

A suspension of 8.0 g. of 10 - (2¹ - piperazinylethyl) - 2 - trifluoromethylphenothiazine, 1.8 g. of potassium carbonate and 1.6 g. of allyl chloride in 100 ml. of aqueous ethanol is stirred at reflux for three hours. After working up as described in Example 13, crystals of 10 - [2¹ - (N - allylpiperazinyl) - ethyl]-2 - trifluoromethylphenothiazine dihydrochloride are obtained.

EXAMPLE 16.

A suspension of 13.4 g. of 2-trifluoromethylphenothiazine, 2.1 g. of sodium amide and 12.5 g. of 3 - chloro - 1 - (N - phenylpiperazinyl) - propane in 250 ml. of toluene is heated at reflux for eight hours. After working up as described in Example 1, crystals of 10 - [3¹ - (N - phenylpiperazinyl) - propyl]-2 - trifluoromethylphenothiazine maleate are recovered.

EXAMPLE 17.

A suspension of 26.7 g. of 2 - trifluoromethylphenothiazine in 600 ml. of toluene with 4.5 g. of sodium amide is heated at reflux and then reacted for six hours with 35.2 g. of 4-carbobenzoxy - 1 - (ω - chloropropyl) - 2,5-diethylpiperazine, prepared by reacting N-carbobenzoxy - 2,5 - diethylpiperazine with γ-chloropropyl bromide in benzene with sodium amide. The reaction mixture containing 10-[3¹ - N - carbobenzoxy - 2¹¹,5¹¹ - diethylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine is washed with water and treated with dilute hydrochloric acid. The acid extracts are warmed briefly, cooled and treated with sodium hydroxide solution. The separated base is taken up in ethyl acetate, dried and micromolecularly distilled to give the thick base, 10 - [3¹ - (2¹¹,5¹¹ - diethylpiperazinyl)-propyl] - 2 - trifluoromethylphenothiazine.

A solution of 3.2 g. of the base in 75 ml. of benzene is heated at reflux with 1.2 g. of isocrotonyl chloride with sodium carbonate for several hours. The reaction mixture is treated with dilute hydrochloric acid after neutralization. The produce is taken up in ethyl acetate, dried and reacted with maleic acid to give 10-[3¹ - (N - isocrotonyl - 2¹¹,5¹¹ diethylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine dimaleate.

Another solution of 3.2 g. of the base in 75 ml. of benzene is reacted with 1.5 g. of dichloroacetyl chloride as above to give the monohydrochloride salt of 10 - [3¹ - (N - dichloroacetyl - 2¹,5¹ - diethylpiperazinyl)-propyl] - 2 - trifluoromethylphenothiazine.

EXAMPLE 18.

A suspension of 2.7 g. of 10 - (3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine (Example 5) in 50 ml. of dimethyl formamide with 1.0 g. of potassium carbonate is stirred while 1.3 g. of benzyl chloride is added. The solution is heated at 80° C. for four hours and poured into an excess of water. The resulting precipitate is washed and extracted into benzene. An excess of hydrogen chloride in ethyl acetate gives 10 - [3¹ - (N - benzylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine dihydrochloride.

Another portion of 2.7 g. of the base is reacted with 1.9 g. of phenethyl bromide, as above, to give 10 - [3¹ - (N - phenethylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine dihydrochloride.

Another portion (2.7 g.) is alkylated with 2.2 g. of ω - phenylbutyl bromide to give the N - ω - phenylbutyl analogue.

The base (5.4 g.) is alkylated with 2.6 g. of thenyl chloride as above. The dimaleate salt of 10 - [3¹ - (N - thenylpiperazinyl)-propyl] - 2 - trifluoromethylphenothiazine is obtained by reacting the crude base with an excess of maleic acid in ethyl acetate solution.

EXAMPLE 19.

A solution of 2.8 g. of 10 - (2¹ - methyl-3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine (Example 10) and 1.6 g. of cyclopentylpropionyl chloride in 50 ml. of benzene is heated at reflux for three hours. The solid separates to give crystals of 10 - [3¹-(N - cyclopentylpropionylpiperazinyl) - 2¹ methylpropyl] - 2 - trifluoromethylphenothiazine hydrochloride.

Another solution of 2.8 g. of the base is reacted with 1.5 g. of hexahydrobenzoyl chloride, as above, to give the hydrochloride of 10 - [3¹ - (N - hexahydrobenzoylpiperazinyl)-2¹ - methylpropyl] - 2 - trifluoromethylphenothiazine.

The base (2.8 g.) is reacted with 2.0 g. of β-cyclohexylethyl bromide in dimethylformamide and 1.0 g. of potassium carbonate is reacted and the product isolated as described in Example 13, to give the dimaleate salt of 10 - [3¹ - (N - cyclohexylethylpiperazinyl)-2¹ - methylpropyl] - 2 - trifluoromethylphenothiazine.

EXAMPLE 20.

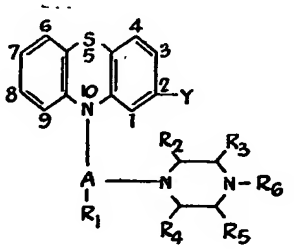
A solution of 3.4 g. of 10 - [3¹ - (N-hydroxybutylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine (Example 5) in 25 ml. of benzene is reacted with 2.3 g. of furoyl chloride in 25 ml. of benzene at reflux for two hours. The hydrochloride of 10 - [3¹-(N - furoyloxybutylpiperazinyl) - propyl] - 2-trifluoromethylphenothiazine separates as a crystalline solid.

EXAMPLE 21.

A suspension of 15.4 g. of 10 - (3¹ - piperazinylpropyl) - 2 - trifluoromethylphenothiazine in 7.5 ml. of concentrated hydrochloric acid and 100 ml. of water is heated to 85° C. The volume of the reaction mixture is brought to 500 ml. with water. Ethanol (100 ml.) is added along with 3.6 g. of potassium cyanate in 25 ml. of water. After refluxing for one hour, the solvent is removed. The cooled reaction mixture is neutralized with ammonium hydroxide. The suspension is extracted with chloroform. The dried chloroform extract is evaporated to leave crystals of 10 - [3¹ - (N-carbamylpiperazinyl) - propyl] - 2 - trifluoromethylphenothiazine.

WHAT WE CLAIM IS:—

1. Chemical compounds of the class consisting of a free base and its nontoxic acid addition salts, the free base having the formula:



in which Y is perfluoroalkyl of 1 to 3 carbon atoms; A is an alkylene chain of from 2 to 6 carbon atoms separating the nitrogen atoms linked thereto by at least two carbon atoms; R_1 is H, R_2, R_3, R_4 and R_5 are methyl, ethyl or hydrogen; R_6 is cycloalkyl having 5 or 6 carbon atoms, cycloalkylalkyl having 6 to 10 carbon atoms, alkenyl having 2 to 6 carbon atoms, dialkylamino - lower - alkyl having 1 to 6 carbon atoms in each of the alkyl portions and 2 to 6 carbon atoms in the lower alkyl portion, hydroxy - lower - alkyl having 2 to 6 carbon atoms in the alkyl portion, hydroxy - lower - alkyl - oxy - lower - alkyl, the lower alkyl portions having 2 to 6 carbon atoms, phenyl, cinnamyl, furoyloxybutyl, furoyl, thenyl, monocyclic aralkyl having 2 to 6 carbon atoms in the alkyl portion, aliphatic acyl having 1 to 6 carbon atoms, alicyclic aliphatic acyl having 7 to 10 carbon atoms,

monocyclic aryl-aliphatic acyl having 6 to 10 carbon atoms, carbomethoxy, carbethoxy, carbobenzoxy, carbamyl, dialkyl carbamyl having 1 to 6 carbon atoms in the alkyl portions and N-phenyl carbamyl, aliphatic acyloxy-lower-alkyl having 1 to 6 carbon atoms in the acyloxyportion and 2 to 6 carbon atoms in the lower alkyl portion, or monocyclic aroyloxy-lower alkyl having 2 to 6 carbon atoms in the lower alkyl portion, the values of Y, A, R_1, R_2, R_3, R_4, R_5 and R_6 being chosen so that in any one compound, when Y is CF_3, A is propylene and R_1, R_2, R_3, R_4 and R_5 are each hydrogen, R_7 is not hydroxy-lower-alkyl having 2 or 3 carbon atoms in the alkyl portion, nor aliphatic acyloxy - lower - alkyl having 1 to 6 carbon atoms in the acyloxy portion and 2 or 3 carbon atoms in the lower alkyl portion.

2. 10 - [3^1 - (N - Hydroxyethoxyethyl-piperazinyl) - propyl] - 2 - trifluoromethyl-phenothiazine.

3. 10 - [3^1 - (N - Formylpiperazinyl)-propyl] - 2 - trifluoromethylphenothiazine.

4. 2 - Heptafluoropropyl - 10 - [3^1 - (N-hydroxyethylpiperazinyl) - propyl] - phenothiazine.

5. 10 - [3^1 - (N - Carbamylpiperazinyl)-propyl] - 2 - trifluoromethylphenothiazine.

6. 10 - [3^1 - (N - Hydroxyethylpiperazinyl)-2^1 - methylpropyl] - 2 - trifluoromethylphenothiazine.

7. 10 - [3^1 - (N - Acetoxyethylpiperazinyl)-2^1 - methylpropyl] - 2- trifluoromethylphenothiazine.

8. 10 - (Piperazinylalkyl) - perfluoroalkyl-phenothiazine derivatives as defined in Claim 1 when produced in accordance with any of Examples 1 to 21.

9. Process for the preparation of 10 - (piperazinylalkyl) - perfluoroalkylphenothiazine derivatives as defined in Claim 1 substantially as hereinbefore described with reference to any of Examples 1 to 21.

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Reference has been directed, in pursuance of Section 8 of the Patents Act, 1949 to specification No. 857,547 and reference has been directed in pursuance of Section 9, subsection (1) of the Patents Act, 1949 to Patent No. 833,474.

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